Correction of endothelial dysfunction in patients with type 2 diabetes mellitus, diabetic kidney disease and non-alcoholic steatohepatitis

Abstract. Background. Non-alcoholic fatty liver disease and chronic kidney disease are public health concerns worldwide due to their increasing prevalence, adverse prognosis, and health care burden. The purpose of the study was to determine the probable effect of a combination of metformin, rosuvastatin, essential phospholipids and quercetin on the blood lipids, endothelial function, fibrinolysis system and platelet hemostasis, which are factors for the progression of nonalcoholic steatohepatitis. Materials and methods. Studies were performed on the dynamics of treatment in 60 patients with non-alcoholic fatty liver disease, type 2 diabetes mellitus and diabetic kidney disease (stage I–III). Depending on the prescribed treatment at random, the examined patients were divided into 2 groups. Twenty-eight persons of the first group received a low-calorie diet with dietary restrictions, essential phospholipids, metformin hydrochloride, rosuvastatin. Thirty-two patients from the second group received quercetin in addition to similar dietary recommendations, essential phospholipids, hypoglycemic and hypolipidemic therapy. The mean age of patients was 53.80 ± 3.52 years. The comparison group consisted of 30 healthy individuals of the corresponding age. Results. To evaluate the degree of endothelial-protective effect of quercetin on the background of the recommended protocol therapy, markers of endothelial dysfunction, fibrinolysis and platelet hemostasis were studied. NO content significantly reduced (1.7 times) in patients of group 2 before treatment, increased by 1.5 times (p < 0.05). This can be explained by the effect of quercetin, as well as the use of metformin, which reduces the degree of insulin resistance and the level of hyperlipidemia. Conclusions. The effectiveness of a combination therapy for non-alcoholic steatohepatitis and type 2 diabetes mellitus with diabetic kidney disease using essential phospholipids, statins and metformin with the addition of quercetin is higher than that of traditional therapy, as it significantly restores the functional state of the endothelium, eliminates the phenomena of hypercoagulation syndrome without the additional prescription of antiplatelet agents. Keywords: type 2 diabetes mellitus; diabetic kidney disease; non-alcoholic steatohepatitis; quercetin

Introduction

Non-alcoholic fatty liver disease (NAFLD) has a global prevalence of 25 % and is a leading cause of cirrhosis and hepatocellular carcinoma. NAFLD encompasses a disease continuum from steatosis with or without mild inflammation (non-alcoholic fatty liver) to non-alcoholic steatohepatitis (NASH), which is characterized by necroinflammation and faster fibrosis progression than non-alcoholic fatty liver. NAFLD has a bidirectional association with components of the metabolic syndrome, and type 2 diabetes mellitus (DM) increases the risk of cirrhosis and related complications [1]. NAFLD is the leading cause of chronic liver disease in the Western world. The excess mortality in NAFLD patients is strongly related to extrahepatic comorbidities. Recently, an association between NAFLD and chronic kidney disease (CKD) has been reported in various populations [2]. NASH is the inflammatory subtype of NAFLD and is associated with disease progression, development of cirrhosis, and need for liver transplant. Despite its importance, NASH is underrecognized in clinical practice [3, 4]. NASH is a chronic
and progressive liver disease characterized by hepatocyte steatosis and inflammation [5, 6]. It has been proven that the degree of NASH activity increases in proportion to the degree of obesity.

DM is on the rise worldwide, with a prevalence in adults in 2017 being 8.8 % of the world population, with the anticipation of a further increase to 9.9 % by 2045. In total numbers, this reflects a population of 424.9 million people with diabetes worldwide in 2017, with an estimate of a 48 % increase to 628.6 million by 2045 [7, 8]. Depending on age, global diabetes prevalence is about 5, 10, 15 and close to 20 %, respectively, for the age groups 35–39, 45–49, 55–59 and 65–69 years. On a global scale, diabetes hits particularly middle-aged people between 40 and 59 years, which causes serious economic and social implications. Furthermore, diabetes affects especially low- and middle-income countries, as 77 % of all people with diabetes worldwide live there. In addition to overt diabetes, an estimated 352.1 million people worldwide are at risk of diabetes, i.e. have defined pre-diabetes, a figure which is anticipated to rise to 531.6 million by 2045 [9].

DM is a major public health challenge and diabetic kidney disease (DKD), a broader diagnostic term than diabetic nephropathy, is the leading cause of chronic kidney disease and end-stage kidney disease [10]. A better understanding of the underlying pathophysiological mechanisms of DKD, and recent clinical trials testing new therapeutic interventions have shown promising results to control this epidemic. Given the global health burden of DKD, it is extremely important to prioritize prevention, early recognition, referral, and aggressive management of DKD in the primary care setting [11]. DKD is the main cause of mortality in patients with DM [12], the leading cause of end-stage renal disease in the world [13], which occurs in patients with DM without long-term adequate glycemic control.

According to C.B. Marshall, the prevalence of DKD remains stable despite efforts to lower glucose levels and counteract the effects of the renin-angiotensin-aldosterone system [14]. R.Z. Alicic emphasizes that DKD is the main complication of type 2 DM, which affects 40 % of patients [11].

The purpose of the study was an elucidation of the possible influence of a combination of metformin, rosvastatin, essential phospholipids and quercetin on the state of the blood lipid spectrum, the functional state of the endothelium, the fibrinolysis system and the platelet link of hemostasis, which are factors for the progression of NASH and DKD.

Material and methods

Sixty patients with NASH, type 2 DM and DKD (stage I–IV) were enrolled in the trial. Among them, there were 48 patients (80.0 %) with mild NASH, 12 (20.0 %) had moderate NASH. Type 2 DM in all patients with NASH was of moderate severity. Fifteen (25.0 %) patients with type 2 DM were compensated, 45 (75.0 %) were subcompensated. All patients with NASH and type 2 DM had DKD: 21 (35.0 %) had DKD stage I–II, 20 people were with DKD stage III (33.3 %), 19 had DKD stage IV (31.7 %). Fifteen (25.0 %) people were diagnosed with degree I–II secondary hypertension of renal origin, 11 (18.3 %) had essential hypertension stage I–II, degree I–II. In addition to type 2 DM and DKD with hypertension, patients with NASH at the time of inclusion in the study did not have any acute or other chronic general somatic pathology in the phase of exacerbation or decompensation, pregnancy.

Depending on the prescribed treatment, the participants were randomly divided into 2 groups. Twenty-eight persons of the first group received a hypocaloric diet, essential phospholipids (EPL), metformin hydrochloride, rosvastatin. The second included 32 patients who received quercetin in addition to similar dietary recommendations, EPL, hypoglycemic and hypolipidemic therapy.

The comparison group consisted of 30 healthy individuals (HI) of the corresponding age.

The average age of the patients was 53.80 ± 3.52 years. Diagnosis of NASH was made according to the unified clinical protocol approved by the Order of the Ministry of Health of Ukraine No. 826 dated November 6, 2014, in the presence of exclusion criteria for chronic diffuse liver diseases of viral, autoimmune, medicinal, toxic etiology, hereditary pathology as causes of the development of cytolyis, cholestasis, mesenchymal inflammation. The results of ultrasonography on the ultrasound scanner Ultima PA (Radmyr, Kharkiv, Ukraine) and biochemical steatotest (SteatoTest, ASH and NASH-Test (BioPredictive, France)) helped determine the degree of liver steatosis and its nature (alcoholic or non-alcoholic).

Diagnosis of type 2 DM was made in accordance with the unified clinical protocol approved by the Order of the Ministry of Health of Ukraine No. 1118 dated December 21, 2012. Diagnosis and treatment of DKD were carried out according to the recommendations from the clinical guidelines of the Institute of Nephrology of the National Academy of Sciences of Ukraine (2012). Glomerular filtration rate was evaluated using the calculator of the Institute of Nephrology of the National Academy of Sciences of Ukraine based on the three average indicators: creatinine clearance according to the Cockcroft-Gault formula, MDRD and CKD-EPI.

In the dynamics of treatment, the blood content of total lipids, total cholesterol (TC), triacylglycerols (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol was analyzed using diagnostic kits from the Simko Ltd company (Lviv, Ukraine). Endothelial functions were investigated non-invasively by determining endothelium-dependent vasodilation (EDDV) of the brachial artery (BA) using a sample with reactive hyperemia on the Aloka-4000 device (Japan). Measurements were performed three times according to the standard method of D.S. Celermajer and co-author in the modification of P.G. Kravchun with co-authors, as well as by the content of stable blood NO metabolites (nitrates, nitrates) using the method of L.C. Green et al. by enzyme-linked immunosorbent assay, the number of desquamated (peeled) endothelial cells. The total (TFA), enzymatic (EFA) and non-enzymatic fibrinolytic activity (NEFA) of the blood was studied with the help of sets of reagents from the Simko Ltd company (Lviv, Ukraine) according to N. Tits.

The aggregation ability of platelets was studied on a platelet aggregation analyzer (Tr) AP2110 (Solar, Belarus) by the turbidimetric method. We determined the degree of spontaneous (SPA) and induced platelet aggregation.
(IPA) using adenosine diphosphate (ADP) at a concentration of $1.0 \times 10^4$ M, the time of development of complete aggregation, the rate of platelet aggregation, the number of platelets, the threshold of sensitivity of platelets to the inducer and the incidence of disaggregation when exposed to an aggregation inducer.

The research was carried out in compliance with the main provisions of the GSR (1996), the Council of Europe Convention on Human Rights and Biomedicine (dated April 4, 1997), the WMA Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects (1964–2013), the Order of the Ministry of Health of Ukraine No. 690 dated September 23, 2009, No. 616 dated August 3, 2012.

Before analyzing the statistical hypotheses, the normality tests for the distribution of values in randomized samples were performed by determining the coefficients of asymmetry and kurtosis using the Hahn-Shapiro-Wilk test. The probability of the difference of the arithmetic mean and its error between the study groups was determined using a two-samples unpaired Student’s t-test. The difference was considered probable at a significance level of $p < 0.05$. Student’s t-test was applied only in case of a normal distribution under equality of general variances of the compared samples, which was checked using Fisher’s F-test. In other cases, the non-parametric Mann-Whitney rank test was used to compare the obtained results. The probability of changes during treatment in case of a normal distribution in the samples was determined by the Student’s paired test, in other cases — by the non-parametric paired Wilcoxon T-test. To identify the effectiveness of treatment programs, we used the method of calculating the odds ratio and determining its 95% confidence interval with the Past3 software. Statistical analysis of the obtained results was carried out using software packages Statistica for Windows version 8.0 (StatSoft Inc., USA), Microsoft Excel 2007 (Microsoft, USA).

Results

Analysis of indicators reflecting the dynamics of NASH biochemical syndromes and lipidograms demonstrated a higher effectiveness of the additional prescription of quercetin to traditional therapy in patients with type 2 DM and DKD. Thus, the increased blood content of total bilirubin in both groups before treatment (by 1.8 times, $p < 0.05$) significantly decreased in the second group by 1.4 times ($p < 0.05$) due to it as of the unconjugated fraction, which decreased by 1.4 times with the normalization of the indicator, and of the conjugated fraction by 1.4 times ($p < 0.05$) (Table 1).

In group 1, the total bilirubin content decreased by 1.2 times ($p < 0.05$) due to a decrease in the unconjugated fraction by 1.2 times ($p < 0.05$), direct bilirubin only tended to decrease ($p > 0.05$). Under the influence of treatment, the activity of alanine aminotransferase (ALT) in patients of both groups increased before treatment by 3.6 times ($p < 0.05$) decreased by 1.3 and 1.7 times ($p < 0.05$), respectively, with a significant difference between the indicators after treatment in groups ($p < 0.05$).

We found a significant effect of therapy with the addition of quercetin on markers of cholestasis: in particular, the activity of ALT increased by 1.9 times before treatment ($p < 0.05$) and gamma-glutamyl transferase ($\gamma$GT) increased by 1.4 times before treatment ($p < 0.05$), decreased only in group 2 by 1.2 times ($p < 0.05$) without normalization of indicators. And in patients of group 1, indicators of activity of ALT and $\gamma$GT even tended to increase.

Analysis of the effect of a combination therapy on the content of total blood lipids, which increased by 1.5 times before treatment ($p < 0.05$), show its decrease by 1.4 times ($p < 0.05$) in patients of group 2 and by 1.2 times ($p < 0.05$) in group 1, with the presence of significant difference between the indicators after treatment ($p < 0.05$). The blood total cholesterol increased by 1.7 times before treatment ($p < 0.05$), after treatment decreased by 27.6 % ($p < 0.05$) in the second group, and in the first group by 10.5 % ($p < 0.05$), with the presence of significant intergroup difference ($p < 0.05$). The blood content of TG, which exceeded the reference values by 1.9 times before treatment, after treatment decreased by 43.6 % in group 2 with normalization of the indicator against a drop of 11.3 % in group 1 ($p < 0.05$). The authors also noted a positive effect of quercetin in relation to the blood content of LDL cholesterol increased by 1.8 times ($p < 0.05$) before treatment: a decrease after treatment was 1.7 times ($p < 0.05$) in the second group and 1.3 times ($p < 0.05$) in group 1 (Table 1).

**Table 1. Markers of liver damage and blood lipids in a combined course of non-alcoholic steatohepatitis and DKD in patients with type 2 diabetes before and after treatment ($M \pm m$)**

<table>
<thead>
<tr>
<th>Indicators</th>
<th>HI, n = 30</th>
<th>Group 1, n = 28 Before</th>
<th>After</th>
<th>Group 2, n = 32 Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin, μmol/l</td>
<td>19.12 ± 1.27</td>
<td>34.25 ± 1.21*</td>
<td>29.03 ± 1.19***</td>
<td>34.30 ± 1.27*</td>
<td>22.11 ± 1.24***</td>
</tr>
<tr>
<td>ALT, mmol/l</td>
<td>0.42 ± 0.05</td>
<td>1.51 ± 0.16*</td>
<td>1.13 ± 0.08***</td>
<td>1.52 ± 0.17*</td>
<td>0.89 ± 0.06***</td>
</tr>
<tr>
<td>γGT, mmol/l</td>
<td>5.06 ± 0.17</td>
<td>7.22 ± 0.14*</td>
<td>7.63 ± 0.15*</td>
<td>7.25 ± 0.16*</td>
<td>6.08 ± 0.13***</td>
</tr>
<tr>
<td>Total lipids, mmol/l</td>
<td>5.87 ± 0.11</td>
<td>8.85 ± 0.43*</td>
<td>7.43 ± 0.25***</td>
<td>8.86 ± 0.22*</td>
<td>6.35 ± 0.14***</td>
</tr>
<tr>
<td>TC, mmol/l</td>
<td>4.38 ± 0.10</td>
<td>7.26 ± 0.21*</td>
<td>6.50 ± 0.10***</td>
<td>7.28 ± 0.16*</td>
<td>5.27 ± 0.13***</td>
</tr>
<tr>
<td>TG, mmol/l</td>
<td>1.47 ± 0.03</td>
<td>2.75 ± 0.07*</td>
<td>2.44 ± 0.05***</td>
<td>2.73 ± 0.06*</td>
<td>1.54 ± 0.03***</td>
</tr>
<tr>
<td>HDL, mmol/l</td>
<td>1.29 ± 0.04</td>
<td>0.92 ± 0.03*</td>
<td>0.98 ± 0.02*</td>
<td>0.92 ± 0.02*</td>
<td>1.23 ± 0.01***</td>
</tr>
<tr>
<td>LDL, mmol/l</td>
<td>2.43 ± 0.02</td>
<td>4.42 ± 0.33*</td>
<td>3.53 ± 0.21***</td>
<td>4.41 ± 0.34*</td>
<td>2.59 ± 0.19***</td>
</tr>
</tbody>
</table>

Notes (here and in Table 2): the difference is probable in comparison: * — with HI ($p < 0.05$); ** — with the indicator before treatment ($p < 0.05$); *** — with control group after treatment ($p < 0.05$).
A combination therapy with the inclusion of quercetin contributed to a significant increase in the blood level of HDL (by 1.3 times; p < 0.05) with the normalization of the indicator after the treatment, while traditional therapy in this cohort did not result in any probable changes (Table 1). Quercetin in combination with rosuvastatin, metformin and EPL, each of which has hypolipidemic properties, potentiates their effect and, by the totality of the impact, maximally reduces serum content of total lipids, cholesterol, TG, LDL cholesterol, restores the HDL pool and exceeds intensity of influence of a traditional combination of hypolipidemic agents without quercetin.

To evaluate the degree of endothelium-protective effect of quercetin against the background of therapy recommended by the protocol, markers of endothelial dysfunction, fibrinolysis and indicators of platelet hemostasis were determined (Table 2). Thus, significantly reduced (by 1.7 times) NO content in patients of the first group before treatment increased not significantly, and in the second group — by 1.5 times (p < 0.05), which can be explained by the effect of quercetin as an endotheliotector, as well as the use of metformin, which reduces the degree of insulin resistance.

EDDV BA significantly reduced in patients of both groups before treatment (by 1.7 times), after treatment increased by 1.8 times (p < 0.05) only in group 2 and reached normative values, which is evidence of restoration of vascular tone (Table 2). Before treatment, the number of circulating endothelial cells (CEC) in patients of both groups exceeded the standard indicators by 1.9 times (p < 0.05). At the same time, the amount of CEC decreased probably in response to the treatment: in group 1 — by 14.4 %, group 2 — by 38.2 % (p < 0.05), with the presence of a probable intergroup difference (p < 0.05) and actual normalization in patients of group 2 (Table 2). The obtained results indicate that both statins, EPL, and quercetin have a significant endothelial protective effect, however, the effect of quercetin is decisive, and it is achieved during a relatively short period of use.

Discussion
Chronic kidney disease secondary to DM has become the main cause of end-stage renal disease in Ukraine [15]. It has been reported that 20–40 % of patients with DM will eventually develop kidney damage [16, 17]. NAFLD is a chronic metabolic disease closely related to insulin resistance and one of the causes of CKD [18]. Furthermore, NAFLD is associated with an increased risk of type 2 DM [19] and increased prevalence and morbidity of chronic kidney disease [20].

The relationship between NAFLD and CKD is bidirectional in patients with type 2 DM [21]. The same pathogenic mechanisms between chronic kidney disease and NAFLD were revealed, such as excessive oxidative stress, out-of-control renin-angiotensin-aldosterone system, and changes in intestinal flora [22].

The endothelium-protective mechanism of statins is a proven pleiotropic effect for representatives of the entire group, as well as the stimulating effect of statins on fibrinolysis. However, a comparative study on the impact of a combination therapy on fibrinolytic activity shows significant advantages of the addition of quercetin over traditional therapy as a whole (Table 2). TFA, which was significantly inhibited before treatment (by 1.2 times) in patients of the second group, increased by 1.2 times after treatment (p < 0.05), while in the control group has not changed. EFA decreased before treatment by 1.9 times, after treatment increased by 1.7 times (p < 0.05) against 1.2 times (p < 0.05) in the controls. NEFA compensatory activated before treatment (by 1.5 times), after treatment in the second group probably decreased by 1.3 times (p < 0.05), which had a positive overall effect regarding the optimization of blood flow in patients with NASH on the background of type 2 DM and DKD (Table 2).

We also found a positive pleiotropic effect of quercetin on indicators of platelet hemostasis, which is associated with the functional state of the endothelium. The degree of SPA, which was significantly increased (by 3.1 times) before treatment, decreased after treatment by 10.6 and 45.1 % (p < 0.05) in groups 1 and 2, respectively, which indicates a powerful anti-aggregation effect of quercetin. The degree of ADP-IPA in the examined patients was increased by 2.6 times (p < 0.05) before treatment. When platelet aggregation was induced after treatment in both groups, indicators decreased by 1.3 and 1.9 times (p < 0.05), respectively. Platelet aggregation rate decreased only in group 2 by 2.2 times (p < 0.05),

Table 2. Indicators of the functional state of the endothelium, fibrinolysis, and platelet hemostasis in patients with a combined course of non-alcoholic steatohepatitis and type 2 diabetes mellitus with DKD in the dynamics of treatment (M ± m)

<table>
<thead>
<tr>
<th>Indicators</th>
<th>HI, n = 30</th>
<th>Group 1, n = 28</th>
<th>Group 2, n = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
</tr>
<tr>
<td>Blood NO, μmol/l</td>
<td>21.29 ± 1.25</td>
<td>12.63 ± 1.45*</td>
<td>13.47 ± 1.21*</td>
</tr>
<tr>
<td>EDDV BA, %</td>
<td>14.15 ± 1.03</td>
<td>8.34 ± 1.32*</td>
<td>10.12 ± 1.15*</td>
</tr>
<tr>
<td>CEC, × 10³/l</td>
<td>3.03 ± 0.17</td>
<td>5.71 ± 0.14*</td>
<td>4.89 ± 0.12***</td>
</tr>
<tr>
<td>TFA, E440/ml/h</td>
<td>1.68 ± 0.03</td>
<td>1.35 ± 0.03*</td>
<td>1.42 ± 0.02*</td>
</tr>
<tr>
<td>NEFA, E440/ml/h</td>
<td>0.48 ± 0.02</td>
<td>0.72 ± 0.03*</td>
<td>0.67 ± 0.02*</td>
</tr>
<tr>
<td>EFA, E440/ml/h</td>
<td>1.20 ± 0.02</td>
<td>0.63 ± 0.02*</td>
<td>0.75 ± 0.02***</td>
</tr>
<tr>
<td>SPA, %</td>
<td>2.10 ± 0.13</td>
<td>6.52 ± 0.15*</td>
<td>5.81 ± 0.13***</td>
</tr>
<tr>
<td>IPA, %</td>
<td>21.32 ± 1.13</td>
<td>54.51 ± 2.72*</td>
<td>43.27 ± 2.41***</td>
</tr>
<tr>
<td>AR, %/min</td>
<td>25.47 ± 1.34</td>
<td>61.27 ± 2.23*</td>
<td>56.53 ± 2.15*</td>
</tr>
<tr>
<td>AT, s</td>
<td>135.00 ± 6.50</td>
<td>58.63 ± 5.84*</td>
<td>71.92 ± 4.83***</td>
</tr>
</tbody>
</table>
and aggregation time increased by 1.2 and 2.1 times, respectively (p < 0.05). The obtained data indicate that the effect of quercetin on the aggregation ability of platelets probably exceeds that of a combination therapy without direct antiplatelet agents, which ensures optimal blood flow and blood supply to both the liver and kidneys.

Conclusions
A combination therapy for non-alcoholic steatohepatitis and type 2 DM with diabetic kidney disease using essential phospholipids, statins and metformin with the addition of quercetin is more effective than traditional treatment. It contributes to a significant reduction in markers of NASH exacerbation (cytolysis, cholestasis), optimization of blood lipids with a decrease in the content of low-density lipoprotein cholesterol, total cholesterol and triacylglycerols, a probable increase in the level of high-density lipoproteins, restores the functional state of the endothelium (contributes to a decrease in the number of desquamated endothelial cells, an increase in the endothelium-dependent vasodilation in the brachial artery, the content of nitrogen monoxide in the blood), eliminates the phenomena of hypercoagulation syndrome without additional prescription of antiaggregants as a result of stimulation of total and enzymatic fibrinolytic activity of the blood, inhibition of spontaneous and induced aggregation of platelets.

References


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Корекція ендотеліальної дисфункції в пацієнтів із цукровим діабетом 2-го типу, діабетичною хворобою нирок та неалкогольним стеатогепатитом

Резюме. Актуальність. Неалкогольна жирова хвороба печінки і хронічна хвороба нирок належать до поширених патологічних станів, мають негативний прогноз і створюють тягар для системи охорони здоров'я. Мета дослідження: визначити вплив комплексного лікування метформіном, розувастатином, есенціальними фосфоліпідами та кверцетином на стан ліпідного спектра крові, функцію ендотелію, систему фібринолізу та тромбоцитарний гемостаз, які є факторами прогресування неалкогольного стеатогепатиту і хронічної хвороби нирок.

Матеріали та методи. Вивчено динаміку лікування в 60 осіб із неалкогольним стеатогепатитом, цукровим діабетом 2-го типу та діабетичною хворобою нирок I–ІІІ стадій. Залежно від призначеного лікування за випадковою ознакою обстежених пацієнтів було розподілено на дві групи. Перша група (n = 28) отримувала низькокалорійну дієту, есенціальні фосфоліпіди, метформіну гідрохлорид, розувастатин. Пацієнти другої групи (n = 32), окрім аналогічних дієтичних рекомендацій, есенціальних фосфоліпідів, гіпохолестеринічної та гіполіпідемічної терапії, додатково отримували кверцетин. Середній вік хворих дорівнював 53,80 ± 3,52 року.

Групу порівняння становили 30 здорових осіб відповідного віку. Результати. Для перевірки ступеня ендотеліопротекторної дії кверцетину на тлі терапії визначали маркери ендотеліальної дисфункції, фібринолізу та тромбоцитарного гемостазу. У пацієнтів другої групи вірогідно, в 1,5 раза (p < 0,05), збільшився рівень оксиду азоту, що можна пояснити впливом кверцетину як ендотеліопротектора, а також застосуванням метформіну, що знижує інсулінорезистентність, сприяє зменшенню рівня гіперплідемії та імовірності відкладення проатерогенних фракцій субендотелію.

Висновки. Ефективність комбінованої терапії неалкогольного стеатогепатиту, цукрового діабету 2-го типу та діабетичного ураження нирок з використанням есенціальних фосфоліпідів, статинів та метформіну із додаванням кверцетину є вищою за таку традиційну терапію, оскільки значно зменшує рівень маркерів загострення, відновлює функціональний стан ендотелію, усуняє явища гіперкоагулентного синдрому без додаткового призначення антагопротеїну.

Ключові слова: цукровий діабет 2-го типу; діабетична хвороба нирок; неалкогольний стеатогепатит; кверцетин